REMARKS

Applicants respectfully request reconsideration of this application in view of the comments that follow.

Status of the Claims

Claims 137-139 are pending. No claims are amended, canceled, or added presently. Upon entry of this paper, therefore, claims 137-139 will be pending and under consideration.

Rejection Under 35 U.S.C. § 103(a)

Claims 137-139 stand rejected over WO 02/088186 to Mikayama *et al.* ("Mikayama PCT") or U.S. Patent No. 7,193,064 to Mikayama *et al.* ("Mikayama") in view of U.S. Patent No. 6,998,124 to Erickson-Miller *et al.*, U.S. Patent No. 6,936,698 to Taylor, and U.S. Patent No. 6,376,653 to Holmes *et al.* Office Action at 5-7. Applicants respectfully traverse the rejection.

A key aspect of applicants' claimed invention is an unexpected finding that the claimed antagonistic anti-CD40 antibody exhibits essentially no agonistic activity. This finding would have been surprising because nothing in the cited art even hints at the possibility that a mutation acknowledged to reduce *effector* function also could abolish residual *agonistic* activity,[1] heretofore seen as characteristic of antagonistic anti-CD40 antibodies. In particular, although the cited secondary references discuss at length a loss of effector function on account of S228P and L235E ("PE") mutations, none teaches or suggests how such mutations of the heavy-chain constant region might effect agonistic activity[2] by virtue of the described crosslinking of the antibody to an F_c receptor. *See* Erickson-Miller at col. 11, ll. 48-52, Taylor at col. 6, ll. 60-66, and Holmes at col. 10, ll. 66 – col. 11, ll. 5.

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[1] See Example 15 and Figure 16, which show that, upon administration of 4D11G4PE antibody to cynomolgus monkeys, no increase in IL-12 production is observed. See also the accompany Rule 132 declaration of co-inventor Nobuaki Takahashi. IL-12 is an indicator of CD40 agonistic activity *in vivo*.

[2] According to the present specification (page 39, lines 11-15), "agonistic" activity refers to an action of enhancing binding of a ligand to CD40 expressed on the surface of such cells as B cells, tumor cells or dendritic cells, or an action of providing the CD40-expressing cells with at least one effect which the CD40 ligand makes on the CD40-expressing cells.

As applicants have explained, an antagonistic anti-CD40 antibody holds great promise for therapeutic regulation of cellular immunity and humoral immunity and has therefore been the subject of intense investigation. Nevertheless, anti-CD40 antibody therapy has not been realized heretofore, in part because the art was bereft of an antagonistic antibody that lacks substantial agonistic activity *in vivo*. In the case with anti-CD40 antibodies, any agonistic activity, "however weak it may be, the symptoms [being treated] may worsen in contrast to the desired therapeutic effect." Specification at page 28, lines 3-6. For this reason, "it [has been] important that anti-CD40 antagonistic antibodies have ***no*** activity to induce signals." *Id.* at page 27, lines 27 and 28 (emphasis added).

Nevertheless, the examiner has opined "that both Reddy et al and Newman et al stand for the entry of clenoliximab (with the same antibody IgG4 mutations/modifications) as taught by the prior art and claimed) into clinical trials for treatment." Advisory Action, page 2. Even taken at face value, however, this assertion overlooks the fact that not all antagonistic antibodies suffer from residual agonistic activity, which, even at seemingly minimal levels, can offset nearly *any* perceived therapeutic advantages in the CD40 context. This is so because of the central role and multipotency of CD40 in immune signaling. In this regard see the "Background" section of applicants' specification, discussing the role of CD40 signaling in B- and T-cell proliferation, differentiation, and cytokine production.

Unique to antagonistic anti-CD40 antibodies, therefore, is the fact that the incidence of *any* agonistic activity can give rise to side-effects that undermine perceived "antagonistic" benefit. Accordingly, CD40-based immunotherapy is far more sensitive to residual agnostic activity than are other therapies, such as the one involving clenolimimab.

For this reason, the skilled artisan would not have generalized from PE mutations of clenoliximab (*i.e.*, anti-CD4 antibody) to a like modification in an anti-CD40 antibody, merely on account of clinical trials begun in the former area. Even more so, the person of ordinary skill would have lacked motivation for such an anti-CD40 antibody modification given the fact,

evidenced by Newman,[3] that just 1.5 mg/kg of clenoliximab is accompanied by agonistic activity *in vivo* at a level, albeit acceptable for a anti-CD4 antibody, would have been (and still would be) *un*acceptable for an antagonistic anti-CD40 antibody.

Examiner Gambel does not appear to dispute the results presented or to question their "unexpectedness." Rather, he suggests that "the level of residual agonistic properties may be more of degree than kind." Advisory Action, page 2.

In light of this comment, applicants provide the accompanying Rule 132 declaration of a co-inventor, Dr. Nobuaki Takahashi.[4] The Takahashi Declaration presents evidence, discussed below, underscoring the fact that applicants' claimed invention would be unobvious, within the meaning of Section 103, even were there a nexus suggested in the prior art between F_c receptor crosslinking and loss of agonistic activity. In particular, the Takahashi Declaration documents a reduction in agonist activity with the claimed invention that would have surprised the skilled artisan both (1) in the magnitude of the reduction and (2) in the dosage range over which the reduction pertains.

First, the claimed antibody shows not merely a reduction in agonistic activity but rather an abolition of agonistic activity, even *in vivo*. Example 15 of the present application shows that the claimed 4D11G4PE antibody does not exhibit *any* agonistic activity *in vivo*. These experiments now have been confirmed, with an additional indicator of CD40 agonist activity (IFNγ[5]) and with a higher dose of 4D11G4PE antibody, in an effort to allay any concern on Examiner Gamble's part that the above-discussed, unexpected benefits pertain only at relatively low doses of the antibody alone.

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[3] See accompanying copy of Newman *et al., Clinical Immunology* 98: 164-74 (2001), at Figure 5e on page 171, 2nd column.

[4] Applicants were unable to obtain Dr. Takahashi's signature of the declaration prior to filing of the present reply. However, Applicants will submit an executed version of the Takahashi Declaration shortly.

[5] In Example 15, only IL-12 was assessed as an indicator of agonistic activity. IFNγ also is an indicator of agonistic activity, however. *See* Schönbeck, *et al., Int'l J. Biochem. & Cell Biol.* 32: 687-93 (2000) (appended), which implicates the interaction of CD154 (CD40 ligand) with its receptor (CD40) in the modulation of inflammatory

Indeed, 4D11G4PE antibody was administered at a concentration of 100 mg/kg in the present experiment, compared to a dose of 30 mg/kg in Example 15.[6] From the resultant data it is apparent that the claimed antibody shows no agonistic activity at a concentration of 100 mg/kg.

Second, the claimed antibody exhibits no agonistic activity *in vivo* even at a concentration more than 50-times higher than had been observed in the prior art. Reddy *et al.* of record shows that, in contrast to appliants' invention, the antagonistic anti-CD4 antibody clenoliximab *does* exhibit agonistic activity *in vivo*.[7] Reddy's teachings comport with Newman, which similarly reports that clenoliximab exhibits agonistic activity when administered to chimpanzees at a concentration of just 1.5 mg/kg. Thus, Newman's Figure 5e evidences "a modulation of cell surface CD4 molecules" by clenoliximab.

The examiner alleges that, "[w]hile applicant's relies [*sic*] upon the modulation of clenoliximab in vivo as described by [Reddy] and [Newman] to indicate cross-linking in vivo or at least at higher doses in vivo (versus in vitro); Newman et al. notes that the mechanism for modulation is unknown (e.g., see p. 173, col. 1, para. 1)." Advisory Action, page 2. As a matter of law, however, the mechanism of "modulation" or agonistic activity is immaterial to the probative quality of applicants' evidence of non-obviousness. Regardless of mechanism, in other words, it is uncontroverted on the record that clenoliximab, which has a PE mutation, exhibits agonistic activity *in vivo* even at the relatively low dose of 1.5 mg/kg. Conversely, the incidence of the same PE mutation in an antagonistic anti-CD40 antibody of applicants' invention *abolishes* agonistic activity *in vivo* at a high dose of 100 mg/kg, as shown in the Takahashi Declaration. This finding would have been entirely unexpected in view of the prior art illustrated by the Reddy and Newman references.

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responses, such as the induction of adhesion molecule expression of pro-inflammatory cytokines, including IFNγ. See Figure lB and related discussion. Thus, Schönbeck identifies IFNγ as an indicator of CD40 agonistic activity.

[6] The relevant experimental methodology and the detailed results are attested to, in the Takahaski Declaration, "by a person in position to corroborate the facts" (Advisory Action, page 2).

[7] Details of the disclosures of Reddy have been already explained in previous of applicants' submissions filings and are therefore not reiterated here for compactness of the record

The claimed antibody thus manifests properties that, considered together, could not have been reasonably predicted by the ordinary artisan at the time of invention. Withdrawal of the subjection obviousness rejection is justified, therefore.

Obviousness-Type Double Patenting Rejection

Pursuant to the Office Action at page 8, claims 137-139 stand provisionally rejected over claims 1-7 of U.S. application serial No. 11/663,340. Applicants traverse this rejection.

Without acquiescing to the examiner's reasoning or conclusion, the examiner is requested to hold this provisional rejection in abeyance until such time as the claims at issue are deemed otherwise allowable. If any double patenting concern remains at that time, applicants will address the rejection on the merits.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Gambel also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

Respectfully submitted,

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